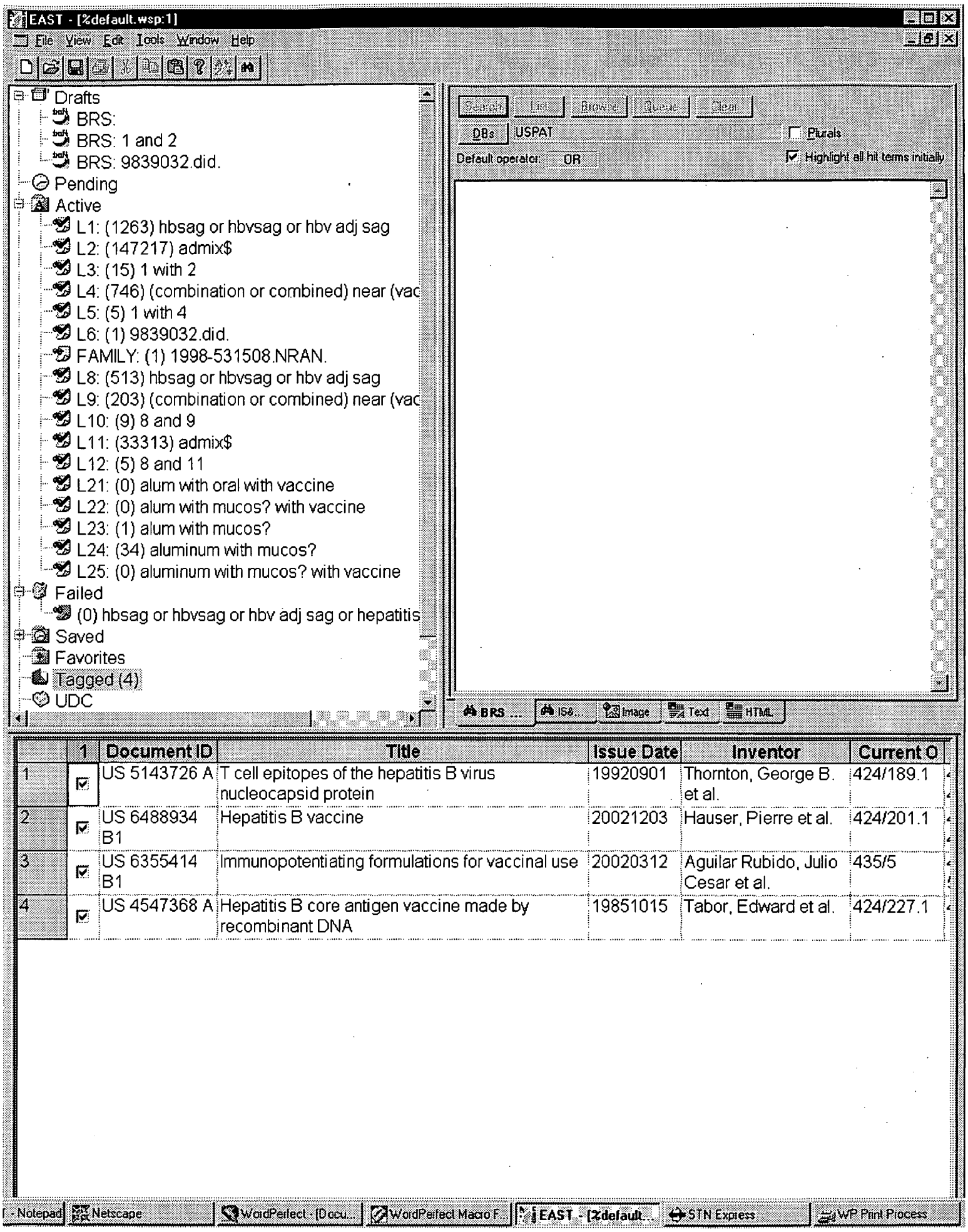
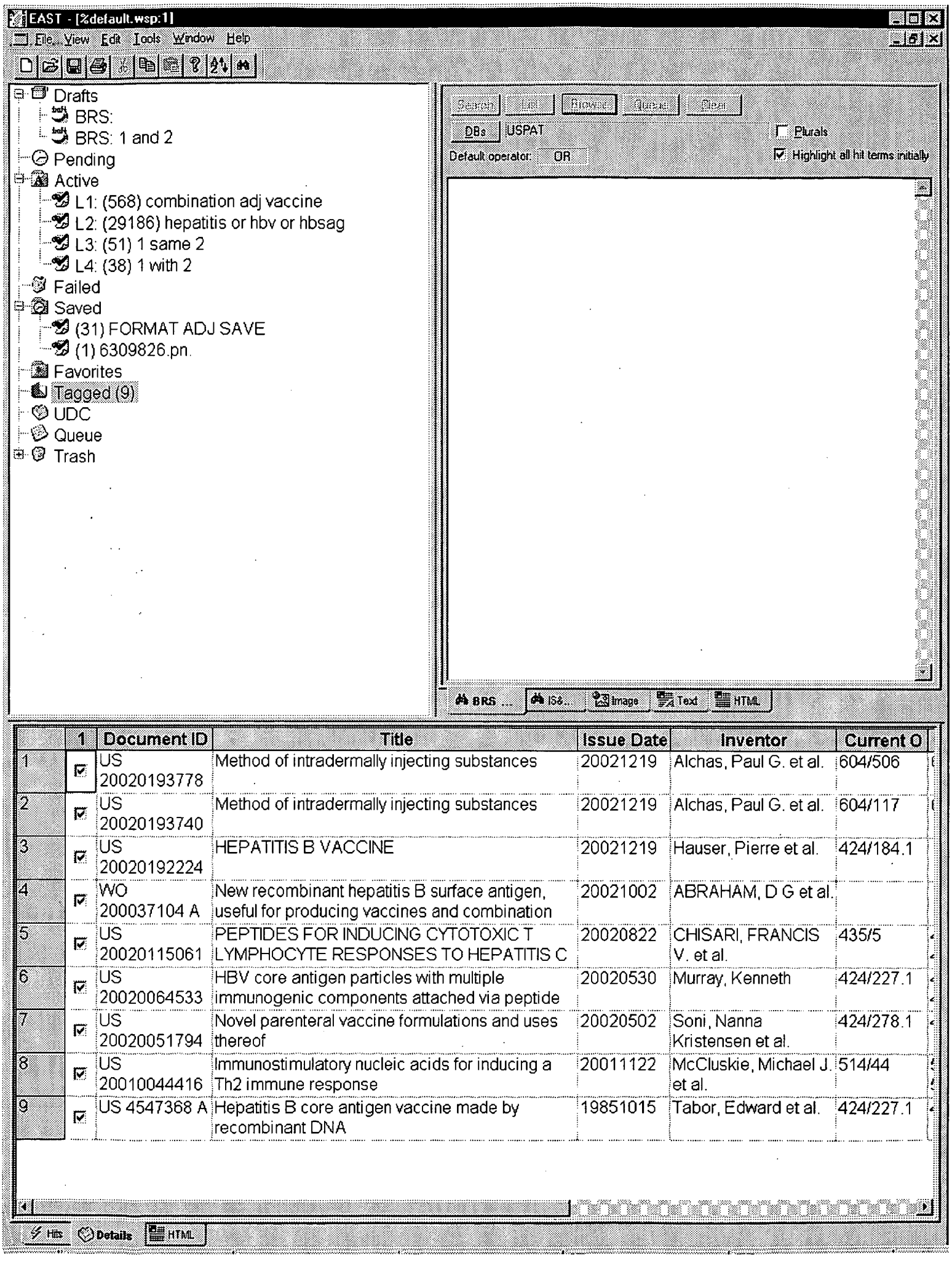
```
     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 17:04:42 ON 28 NOV 2001
L1         39366 S HEPATITIS(W)B(W)SURFACE OR HBSAG
L2         11408 S VIRAL(W)CAPSID OR VIRAL(W)NUCLEOCAPSID OR VLP OR
VIRUS(W)LIKE
L3           135 S L1 AND L2
L4        311864 S VACCIN?
L5            24 S L3 AND L4
L6            14 DUP REM L5 (10 DUPLICATES REMOVED)
L7             3 S PAPILLMAVIRUS
L8         32318 S PAPILLOMAVIRUS
L9           854 S L8 AND L2
L10            4 S L9 AND L1
L11            2 DUP REM L10 (2 DUPLICATES REMOVED)
```

L Number	Hits	Search Text	DB	Time stamp
1	808	(surface adj antigen$1) and nasal	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 12:01
2	3	(surface adj antigen$1) with nasal	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 11:58
3	409	(surface adj antigen$1) and nasal and hepatitis	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 12:01
4	271	(surface adj antigen$1) and nasal and hepatitis and vaccine	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 12:05
5	2	(surface adj antigen$1) and nasal with hepatitis and vaccine	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 12:06
6	2647	(surface adj antigen$1) with hepatitis	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 12:06
7	1	(surface adj antigen$1) with hepatitis with mucos$2	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 12:07
8	276	(surface adj antigen$1) with hepatitis and mucos$2	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 12:15
9	164	(virus adj like particles) and (surface adj antigen$1) with hepatitis and mucos$2	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 12:16
10	1	(virus adj like particles) and (surface adj antigen$1) with hepatitis with mucos$2	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 12:16
11	175	(virus adj like particles) and (surface adj antigen$1) with hepatitis and nasal	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 12:17
12	94	(virus adj like particles) with hepatitis and nasal	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 12:17
13	0	(virus adj like particles) with papailloma and nasal	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 12:17

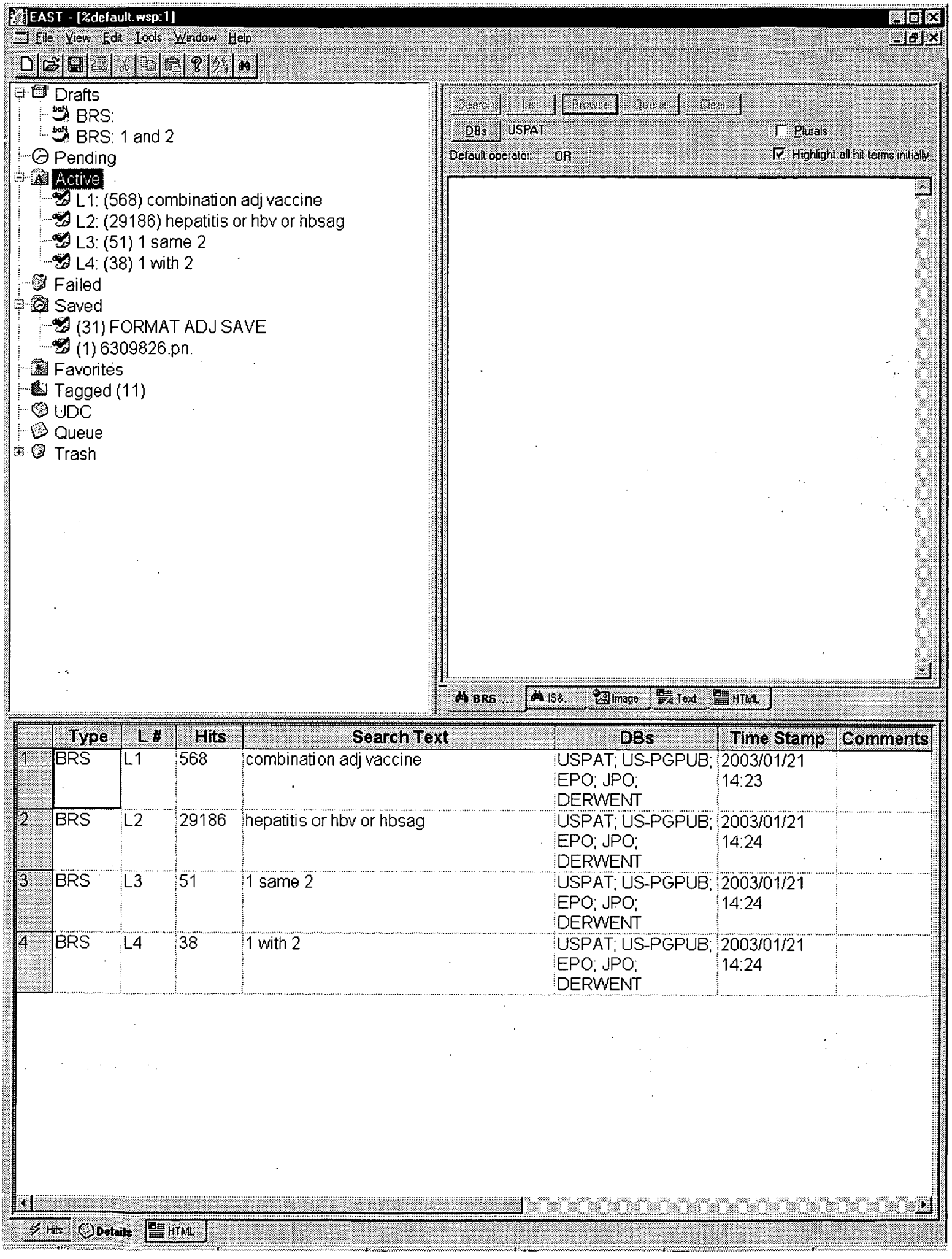
14	0	(virus adj like particles) with papailloma	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 12:18
15	0	(virus adj like particles or VLP) with papaillomavirus	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 12:18
16	119	(virus adj like particles or VLP) with papillomavirus	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 12:19
17	18	(virus adj like particles or VLP) with papillomavirus and nasal	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 12:19
18	0	(virus adj like particles or VLP) with papillomavirus with nasal	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/11/28 12:19



	1	Document ID	Title	Issue Date	Inventor	Current O
1	☑	US 5143726 A	T cell epitopes of the hepatitis B virus nucleocapsid protein	19920901	Thornton, George B. et al.	424/189.1
2	☑	US 6488934 B1	Hepatitis B vaccine	20021203	Hauser, Pierre et al.	424/201.1
3	☑	US 6355414 B1	Immunopotentiating formulations for vaccinal use	20020312	Aguilar Rubido, Julio Cesar et al.	435/5
4	☑	US 4547368 A	Hepatitis B core antigen vaccine made by recombinant DNA	19851015	Tabor, Edward et al.	424/227.1



	1	Document ID	Title	Issue Date	Inventor	Current O
1	☑	US 20020193778	Method of intradermally injecting substances	20021219	Alchas, Paul G. et al.	604/506
2	☑	US 20020193740	Method of intradermally injecting substances	20021219	Alchas, Paul G. et al.	604/117
3	☑	US 20020192224	HEPATITIS B VACCINE	20021219	Hauser, Pierre et al.	424/184.1
4	☑	WO 200037104 A	New recombinant hepatitis B surface antigen, useful for producing vaccines and combination	20021002	ABRAHAM, D G et al.	
5	☑	US 20020115061	PEPTIDES FOR INDUCING CYTOTOXIC T LYMPHOCYTE RESPONSES TO HEPATITIS C	20020822	CHISARI, FRANCIS V. et al.	435/5
6	☑	US 20020064533	HBV core antigen particles with multiple immunogenic components attached via peptide	20020530	Murray, Kenneth	424/227.1
7	☑	US 20020051794	Novel parenteral vaccine formulations and uses thereof	20020502	Soni, Nanna Kristensen et al.	424/278.1
8	☑	US 20010044416	Immunostimulatory nucleic acids for inducing a Th2 immune response	20011122	McCluskie, Michael J. et al.	514/44
9	☑	US 4547368 A	Hepatitis B core antigen vaccine made by recombinant DNA	19851015	Tabor, Edward et al.	424/227.1



	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments
1	BRS	L1	568	combination adj vaccine	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/21 14:23	
2	BRS	L2	29186	hepatitis or hbv or hbsag	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/21 14:24	
3	BRS	L3	51	1 same 2	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/21 14:24	
4	BRS	L4	38	1 with 2	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/21 14:24	

L11 ANSWER 2 OF 2 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999147236 EMBASE
TITLE: Vaccination against infectious agents associated with human cancer.
AUTHOR: Coursaget P.; Munoz N.
CORPORATE SOURCE: P. Coursaget, Faculte de Pharmacie, Lab. Immunol. Maladies Infectieuses, 31 Avenue Monge, F-37200 Tours Cedex, France
SOURCE: Cancer Surveys, (1998) 33/- (355-381).
Refs: 106
ISSN: 0261-2429 CODEN: CASUD7
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
005 General Pathology and Pathological Anatomy
016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The realization that approximately one sixth of all cancers can be attributed to infectious agents opens great perspectives for the prevention and treatment of cancer. This is particularly true for cancers of the cervix, stomach and liver that are very common in developing countries, where they represent 91% of the cancers associated with infectious agents. Today, numerous manufacturers have entered the market of HBV vaccine, and safe and effective HBV vaccines, both plasma derived or recombinant DNA derived, are available. Great progress has been made during the last two decades in controlling HBV infection, but the universal use of HBV vaccine, which will dramatically reduce in future the number of deaths due to cirrhosis and liver cancer, is still a very challenging goal. Therapeutic HBV vaccination of **HBsAg** carriers shows an efficacy similar to that of interferon treatment in reducing the viral replication with the advantage of a lower percentage of side effects and a lower cost. The reduction in viral replication obtained with HBV therapeutic vaccines is expected to be followed by a reduction in the chronic sequelae of HBV infection including liver cirrhosis and liver cancer. Following the encouraging results obtained with both prophylactic and therapeutic **papillomavirus** vaccines in various animal models, much progress has been made in the development of HPV vaccines in the last decade. Phase I- II clinical trials are under way to assess the safety and immunogenicity of various **VLP** based prophylactic vaccines for HPV 11, 16 and 18 and phase III trials to assess their efficacy are being planned. Phase I-II trials have also been carried out or are in progress for therapeutic vaccines against HPV 16 and 18 associated lesions. However, there are still many technical and practical problems that need to be solved before safe, effective and inexpensive HPV vaccines are produced for mass use in the general population. Meanwhile efforts should continue to introduce or improve existing screening programmes for cervical cancer. The successful demonstration in several mouse models that various H pylori vaccines can induce not only protection against infection, but also regression of infection and associated lesions, raises the hope of the development of similar vaccines in humans. However, the relatively poor results so far obtained in other animal models more relevant to humans, such as cats and monkeys and in phase I-II

human trials, indicate that much research is still needed.

L8 ANSWER 15 OF 44 MEDLINE on STN
ACCESSION NUMBER: 2000493897 MEDLINE
DOCUMENT NUMBER: 20398398 PubMed ID: 10938512
TITLE: Diagnosis and management of chronic **hepatitis** C.
AUTHOR: Par A
CORPORATE SOURCE: First Department of Medicine, University Medical School Pecs, Pecs, Hungary.. apar@clinics.pote.hu
SOURCE: CANADIAN JOURNAL OF GASTROENTEROLOGY, (2000 Jul-Aug) 14 Suppl B 83B-88B. Ref: 33
Journal code: 8807867. ISSN: 0835-7900.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001027
Last Updated on STN: 20001027
Entered Medline: 20001019

AB This mini-review is devoted to the main questions of diagnosis, treatment and prevention of chronic **hepatitis** C (CHC). Diagnosis of CHC is based on virological, biochemical and histological findings. The etiology of CHC should be proven by the presence of antibody to **hepatitis** C virus (anti-HCV) and detection of viral nucleic acid (HCV RNA), using qualitative and quantitative polymerase chain reaction or branched chain DNA techniques. Serum aminotransferase levels can reflect the biochemical activity of liver disease, while biopsy is very important in the grading and staging of the pathological process. The generally accepted treatment of CHC is interferon (IFN); however, recently, the **combination** of IFN with the **oral** nucleoside analogue ribavirin has become the therapy of choice, not only for relapsers but also for naive patients. Prevention of **hepatitis** C by **vaccination** is not yet available. Screening blood donors and members of high risk groups, as well as ensuring good public health measures, are imperative to inhibit the spread of HCV.

L39 ANSWER 31 OF 43 MEDLINE on STN
ACCESSION NUMBER: 97116583 MEDLINE
DOCUMENT NUMBER: 97116583 PubMed ID: 8957671
TITLE: Genetically engineered particulate virus-like structures and their use as vaccine delivery systems.
AUTHOR: Roy P
CORPORATE SOURCE: Department of Biochemistry, University of Oxford, UK.
SOURCE: INTERVIROLOGY, (1996) 39 (1-2) 62-71. Ref: 25
Journal code: 0364265. ISSN: 0300-5526.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970327
Last Updated on STN: 19990129
Entered Medline: 19970314

AB The Orbivirus genus within the family Reoviridae consists of nonenveloped architecturally complex viruses. The icosahedral viruses are 810 A diameter in size and are comprised of two protein shells containing seven proteins (VP1-VP7), surrounding a genome of ten double-stranded RNA segments. The prototype virus, bluetongue virus (BTV), is the etiological agent of a disease that can reach epidemic proportions among sheep and cattle. To develop highly protective virus-like particles, we have developed novel baculovirus multigene expression vector systems which have allowed us to coexpress three, four or five BTV genes from single recombinant vectors. The resultant particulate structures resemble BTV virus-like and subvirus-like particles which are structurally and immunologically indistinguishable from the BTV, and preliminary clinical trials have verified this vaccines **safety** and efficacy. Unlike live virus vaccines, VLPs are noninfectious and lack virus (or other) DNA/RNA required for replication. VLPs do not replicate in host cells. However, sheep trials have shown that VLPs are more immunogenic than **subunit vaccines** (viral proteins), or viruses killed by chemical inactivation. In addition, they are effective at eliciting humoral, cell-mediated and mucosal immunities. Virus-like particles (VLPs) are safe to produce and handle. The baculovirus vector and host cells used to make VLPs do not come from mammalian sources (hence they do not contain mammalian-derived pathogens). The multicomponent VLPs have also been utilized as vaccine delivery systems for multiple immunogens including B and T cell epitopes. The expression system described here is a tool which may have a range of applications in industries employing biotechnology to produce vaccines, insecticides, diagnostic and protein reagents.

L37 ANSWER 3 OF 14 MEDLINE on STN
ACCESSION NUMBER: 2001654956 MEDLINE
DOCUMENT NUMBER: 21564617 PubMed ID: 11707303
TITLE: Advances and prospects for **subunit** **vaccines** against protozoa of veterinary importance.
AUTHOR: Jenkins M C
CORPORATE SOURCE: Immunology and Disease Resistance Laboratory, Agricultural Research Service, US Department of Agriculture (USDA), Beltsville, MA 20705, USA.. mjenkins@anri.barc.usda.gov
SOURCE: VETERINARY PARASITOLOGY, (2001 Nov 22) 101 (3-4) 291-310. Ref: 95
Journal code: 7602745. ISSN: 0304-4017.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20011115
Last Updated on STN: 20020417
Entered Medline: 20020416

AB Protozoa are responsible for considerable morbidity and mortality in domestic and companion animals. Preventing infection may involve deliberate exposure to virulent or attenuated parasites so that immunity to natural infection is established early in life. This is the basis for vaccines against theilerosis and avian coccidiosis. Vaccination may not be effective or practical with diseases, such as cryptosporidiosis, that primarily afflict the immune-compromised or individuals with an incompletely developed immune system. Strategies for combating these diseases often rely on passive immunotherapy using serum or colostrums containing antibodies to parasite surface proteins. **Subunit** **vaccines** offer an attractive alternative to virulent or attenuated parasites for several reasons. These include the use of bacteria or lower eukaryotes to produce recombinant proteins in batch culture, the relative **stability** of recombinant proteins compared to live parasites, and the flexibility to incorporate only those antigens that elicit "protective" immune responses. Although **subunit** **vaccines** offer many theoretical advantages, our lack of understanding of immune mechanisms to primary and secondary infection and the capacity of many protozoa to evade host immunity remain obstacles to developing effective vaccines. This review examines the progress made on developing recombinant proteins of Eimeria, Giardia, Cryptosporidium, Toxoplasma, Neospora, Trypanosoma, Babesia, and Theileria and attempts to use these antigens for vaccinating animals against the associated diseases.

L23 ANSWER 26 OF 43 MEDLINE on STN
ACCESSION NUMBER: 97335379 MEDLINE
DOCUMENT NUMBER: 97335379 PubMed ID: 9192045
TITLE: Virus-like particle vaccines for mucosal immunization.
AUTHOR: Estes M K; Ball J M; Crawford S E; O'Neal C; Opekun A A; Graham D Y; Conner M E
CORPORATE SOURCE: Division of Molecular Virology, Department of Medicine, Baylor College of Medicine, Houston, Texas 77030, USA.
CONTRACT NUMBER: AI 24998 (NIAID)
AI 36519 (NIAID)
SOURCE: ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1997) 412 387-95.
Journal code: 0121103. ISSN: 0065-2598.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970908
Last Updated on STN: 19970908
Entered Medline: 19970826

AB Viruses which infect the gastrointestinal tract are well suited for examining the immune response(s) to oral delivery of antigen and exploring the advantages and pitfalls of oral vaccines. We have used recombinant DNA techniques to produce nonreplicating self-assembled virus-like particles (VLPs) from two gastrointestinal viruses, rotavirus and Norwalk virus. Both of these viruses normally cause acute gastroenteritis in man or animals. The VLPs are morphologically and antigenically similar to the native virus and quite stable, features which are advantageous for their use as **subunit vaccines**. In addition, these VLPs could be useful as carriers of foreign epitopes from heterologous pathogens or of drugs which need to be delivered to the gastrointestinal track. This paper briefly **reviews** the properties of these VLPs made in insect cells and data showing their potential as **subunit vaccines** for parenteral or oral delivery.

L18 ANSWER 13 OF 14 MEDLINE on STN
ACCESSION NUMBER: 93029913 MEDLINE
DOCUMENT NUMBER: 93029913 PubMed ID: 1329168
TITLE: **Mucosal** delivery of herpes simplex virus vaccine.
AUTHOR: Bowen J C; Alpar H O; Phillpotts R; Brown M R
CORPORATE SOURCE: Department of Pharmaceutical Sciences, Aston University, Birmingham, UK.
SOURCE: RESEARCH IN VIROLOGY, (1992 Jul-Aug) 143 (4) 269-78.
Journal code: 8907469. ISSN: 0923-2516.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199211
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19930122
Entered Medline: 19921123

AB The **mucosal** route for the production of **mucosal** and systemic herpes simplex virus (HSV) antibodies was investigated using HSV1 **subunit vaccine** administered to guinea pigs. Groups of test animals (n = 13) were dosed, nasally or vaginally and compared with those **injected** subcutaneously (s.c.). The vaccines, in aqueous or gel form, were administered 5 and 3 weeks prior to vaginal challenge with HSV2 suspension. Control infected and non-infected animals were included for comparison. Animals which were vaccinated s.c. were shown to respond to subsequent infection with HSV by the production of serum HSV-specific IgG (and IgA) but negligible amounts of vaginal IgG and IgA. Control non-infected and infected-only groups produced none and only a small amount of vaginal HSV-specific antibodies, respectively. Substantial protection against HSV2 infection of the female guinea pig genital tract was provided by s.c. immunization with HSV vaccine. Protection was evaluated in terms of the reduction of histopathological lesions and clinical signs in vaccinated and control animals. The serum humoral response to nasal delivery in phosphate-buffered saline was comparable, and was superior for vaginal washes to that of parenteral vaccination. The nasally delivered free antigen gave significant ($p < or = 0.05$) reduction in the severity of the disease and higher levels of specific serum and vaginal immunoglobulin antibodies to HSV when compared with non-immunized infected-only controls, probably due to uptake of antigenically intact protein. Vaginal gel treatment slightly reduced the severity of the illness and gave higher humoral responses than those induced by vaginally delivered free antigen. Findings also indicate that these **mucosal** immune responses were produced at a site distant from the site of vaccination, suggesting a common immunological system.

UMENT NUMBER: 21340358 PubMed ID: 11447149
TITLE: Facilitated intranasal induction of mucosal and systemic immunity to mutans streptococcal glucosyltransferase peptide **vaccines**.
AUTHOR: Smith D J; King W F; Barnes L A; Trantolo D; Wise D L; Taubman M A
CORPORATE SOURCE: Department of Immunology, The Forsyth Institute, Boston, Massachusetts 02115, USA.. dsmith@forsyth.org
CONTRACT NUMBER: DE-04733 (NIDCR)
DE-06153 (NIDCR)
SOURCE: INFECTION AND IMMUNITY, (2001 Aug) 69 (8) 4767-73.
Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010827
Last Updated on STN: 20010827
Entered Medline: 20010823

AB Synthetic peptide **vaccines** which are derived from functional domains of Streptococcus mutans glucosyltransferases (GTF) have been shown to induce protective immunity in Sprague-Dawley rats after subcutaneous injection in the salivary gland region. Since mucosal induction of salivary immunity would be preferable in humans, we explored methods to induce mucosal antibody in the rat to the GTF peptide **vaccines** HDS and HDS-GLU after intranasal administration. Several methods of facilitation of the immune response were studied: the incorporation of peptides in bioadhesive poly(D,L-lactide-coglycolide) (PLGA) microparticles, the use of monoepitopic (HDS) or diepitopic (HDS-GLU) peptide constructs, or the use of mucosal adjuvants. Salivary immunoglobulin A (IgA) responses were not detected after intranasal administration of diepitopic HDS-GLU peptide constructs in **alum** or after incorporation into PLGA microparticles. However, significant primary and secondary salivary IgA and serum IgG antibody responses to HDS were induced in all rats when cholera holotoxin (CT) or a detoxified mutant Escherichia coli heat-labile enterotoxin (R192G LT) were intranasally administered with HDS peptide constructs in PLGA. Coadministration of LT with HDS resulted in predominantly IgG2a responses in the serum, while coadministration with CT resulted in significant IgG1 and IgG2a responses to HDS. Serum IgG antibody, which was induced to the HDS peptide construct by coadministration with these adjuvants, also bound intact mutans streptococcal GTF in an enzyme-linked immunosorbent assay and inhibited its enzymatic activity. Thus, immune responses which are potentially protective for dental caries can be induced to peptide-based GTF **vaccines** after **mucosal administration** if combined with the CT or LT R192G mucosal adjuvant.

L8 ANSWER 26 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1999203074 MEDLINE
DOCUMENT NUMBER: 99203074 PubMed ID: 10189191
TITLE: Immunization against **hepatitis** B virus by **mucosal administration** of antigen-antibody complexes.
AUTHOR: McCluskie M J; Wen Y M; Di Q; Davis H L
CORPORATE SOURCE: Loeb Health Research Institute, Ottawa, Canada.
SOURCE: VIRAL IMMUNOLOGY, (1998) 11 (4) 245-52.
Journal code: 8801552. ISSN: 0882-8245.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990614
Last Updated on STN: 19990614
Entered Medline: 19990528

AB Antigen-antibody complexes have been shown to enhance immune responses against several antigens given by parenteral immunization. Herein, we have evaluated the potential of administering such immunostimulatory complexes by a **mucosal** route. **Hepatitis** B surface antigen (HBsAg) complexed with antibodies against HBsAg (anti-HBs) (HBsAg/Ab) was administered to BALB/c mice by **intranasal** inhalation. HBsAg by itself did not induce immune responses, whereas with HBsAg/Ab complexes, both systemic and **mucosal** immune responses were observed and these could be modulated by adjuvants. With HBsAg/Ab (1 or 10 microg), anti-HBs antibodies induced were predominantly of the IgG1 isotype (Th2-like). In contrast, anti-HBs induced by HBsAg/Ab plus cholera toxin (CT) or oligodeoxynucleotides (ODN) containing immunostimulatory CpG motifs (CpG) (1 microg each) were predominantly IgG2a (Th1-like). Results from this study indicate that HBsAg/Ab complexes can induce strong humoral immune responses when delivered by a noninvasive route, whether used alone or in **combination** with other **mucosal** adjuvants.

can't get this article + not prior at anyway

6/7/39
DIALOG(R)File 155:MEDLINE(R)

07934536 94000065 PMID: 8397580

Safety and immunogenicity of a combined hepatitis B virus-Haemophilus influenzae type B vaccine formulation in healthy adults.

Bulkow L R; McMahon B J; Wainwright R B; Parkinson A J; Wainwright K Y; House J

Arctic Investigations Program, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Anchorage, Alaska.

Arctic medical research (FINLAND) Jul 1993, 52 (3) p118-26, ISSN 0782-226X Journal Code: 8602204

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

not clear whether it's DNA or not

We administered a combined preparation of hepatitis B virus (HBV) vaccine and Haemophilus influenzae type b (Hib) conjugate vaccine (meningococcal protein conjugate) to 20 healthy adult volunteers. Participants received two doses of vaccine one month apart, and had serum samples drawn each time they received the vaccine and 1 month after the second dose. In 18 of 19 persons who were positive for antibody to hepatitis B surface antigen (anti-HBs), these levels had a median fold increase of 23.4 (range 0.69 to 270) 1 month after the first dose of vaccine. Anti-HBs levels generally fell slightly one month after the second dose was given. All of the study participants initially had detectable levels of antibody to Hib capsular polysaccharide (anti-PRP), and 19 of the 20 exhibited a median fold increase of 11.2 (range 0.81 to 740) in anti-PRP 1 month after vaccination. Over half (65%) continued to demonstrate increased levels of anti-PRP with the second dose of vaccine. Most participants experienced some slight to moderate discomfort at the injection site. The results indicate that the combined Hib/HBV vaccine produces increased antibody levels in healthy adults who have previously been exposed to these two antigens.

Record Date Created: 19931027

Record Date Completed: 19931027

definitely not mucosal admin

done

1: Arctic Med Res. 1993 Jul;52(3):118-26. Related Articles, Links

Entrez PubMed

PubMed Services

Related Resources

Safety and immunogenicity of a combined hepatitis B virus-Haemophilus influenzae type B vaccine formulation in healthy adults.

Bulkow LR, McMahon BJ, Wainwright RB, Parkinson AJ, Wainwright KY, House J.

Arctic Investigations Program, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Anchorage, Alaska.

We administered a combined preparation of hepatitis B virus (HBV) vaccine and Haemophilus influenzae type b (Hib) conjugate vaccine (meningococcal protein conjugate) to 20 healthy adult volunteers. Participants received two doses of vaccine one month apart, and had serum samples drawn each time they received the vaccine and 1 month after the second dose. In 18 of 19 persons who were positive for antibody to hepatitis B surface antigen (anti-HBs), these levels had a median fold increase of 23.4 (range 0.69 to 270) 1 month after the first dose of vaccine. Anti-HBs levels generally fell slightly one month after the second dose was given. All of the study participants initially had detectable levels of antibody to Hib capsular polysaccharide (anti-PRP), and 19 of the 20 exhibited a median fold increase of 11.2 (range 0.81 to 740) in anti-PRP 1 month after vaccination. Over half (65%) continued to demonstrate increased levels of anti-PRP with the second dose of vaccine. Most participants experienced some slight to moderate discomfort at the injection site. The results indicate that the combined Hib/HBV vaccine produces increased antibody levels in healthy adults who have previously been exposed to these two antigens.

PMID: 8397580 [PubMed - indexed for MEDLINE]

L8 ANSWER 20 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1999008497 MEDLINE
DOCUMENT NUMBER: 99008497 PubMed ID: 9794366
TITLE: CpG DNA is a potent enhancer of systemic and **mucosal** immune responses against **hepatitis** B surface antigen with **intranasal** **administration** to mice.
AUTHOR: McCluskie M J; Davis H L
CORPORATE SOURCE: Loeb Research Institute, Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Canada.
SOURCE: JOURNAL OF IMMUNOLOGY, (1998 Nov 1) 161 (9) 4463-6. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981118

AB **Mucosal** immunity is difficult to induce with subunit **vaccines** unless such **vaccines** are administered with a **mucosal** adjuvant such as cholera toxin (CT); however, CT is toxic in humans. Synthetic oligodeoxynucleotides containing immunostimulatory CpG motifs (CpG) are potent adjuvants for the induction of Th1-like systemic immune responses against parenterally delivered proteins. Here, we show in mice that **intranasal** delivery of **hepatitis** B surface Ag, which alone has no effect, elicits good immune responses when given with CpG oligodeoxynucleotides and/or CT. Overall, CpG is superior to CT for the induction of humoral and cell-mediated systemic immunity as well as **mucosal** immune responses (IgA) at local (lung) and distant (feces) sites. Furthermore, CpG and CT act synergistically, giving stronger responses than those observed with 10 times more of either adjuvant alone. Ab isotypes were predominantly IgG1 (Th2-like) with CT, **mixed** IgG1/IgG2a (Th0) with CpG, and predominantly IgG2a (Th1-like) with CpG and CT together.

5759551

~~suggests~~ teaches combo vaccine w/ LHRH + HBsAg ~~does~~ in microparticles, but does not teach

out 1 mg of each peptide per kg body weight. When delivered in multiple doses, the dosage unit form is conveniently divided into the appropriate amounts per dosage.

Detailed Description Text - DETX (42):

Vaccines which contain cocktails of two or more of the subject peptides enhance immunoefficacy in a broader population and thus provide a better immune response against LHRH. For example, a cocktail of Peptides A, F and H is useful. A preferred cocktail includes Peptides 18, 19, K and H; another includes 32, 19, K and H. Other immunostimulatory synthetic peptide LHRH immunogens are arrived at through modification into lipopeptides so as to provide built-in adjuvanticity for potent vaccines. The immune response to synthetic peptide LHRH immunogens can be improved by delivery through entrapment in or on biodegradable microparticles of the type described by O'Hagan ~~et al. (1991)~~ Vaccine 9:768-771. The immunogens can be encapsulated with or without adjuvant, including covalently attached Pam.sub.3 Cys (see Example 15), and such microparticles can be administered with an immunostimulatory adjuvant such as Freund's Incomplete Adjuvant or alum. The microparticles function to potentiate immune responses to an immunogen and to provide time-controlled release for sustained or periodic responses, for oral administration, and for topical administration [O'Hagan et al.; Eldridge et al. (1991) Molec. Immunol. 28:287-294].

Detailed Description Text - DETX (44):

Serum LHRH can be measured by radioimmunoassay (RIA), enzyme-linked immunoadsorbent assay (EIA) or other convenient method. Antibodies against LHRH are measured by RIA (see Example 2)

LHRH to induce infertility in microparticles w/ & wo/ adjuvant

pression, a problem encountered when
toxin molecules are used to elicit helper T cell responses.

Detailed Description Text - DETX (5):

3. Mixing of T.sub.h Epitope-modified Immunogens to Cause Broad-spectrum Efficacy. The T.sub.h epitopes of the invention are promiscuous but not universal. This characteristic means that the T.sub.h epitopes are reactive in a large segment of an outbred population expressing different MHC antigens (reactive in 50 to 90% of the population), but not in all members of that population. To provide a comprehensive, approaching universal, immune reactivity for the LHRH immunotherapeutic construct, a combination of LHRH constructs with different T.sub.h epitopes can be prepared. For example, a combination of four T.sub.h epitope: LHRH constructs, including promiscuous T.sub.h epitopes from tetanus and pertussis toxins, measles virus F protein and from the HBsAg is particularly effective. On an equimolar basis, this mixture is more broadly effective than any single immunogen in the mixture.

Detailed Description Text - DETX (11):

8. Microparticle Delivery of Modified Immunogens. Immunotherapy regimens which produce maximal i

b.h : LHRH constructs
adjuvanted with aluminum hydroxide was tested. The following is a summary of that experiment. The experimental design is the same as in Example 5 except as indicated otherwise.

Detailed Description Text - DETX (221):
1. Mixing promiscuous T.sub.h : LHRH synthetic peptide constructs provides an efficacious LHRH immunotherapeutic vaccine.

Detailed Description Text - DETX (263):
The HBsAg T.sub.h : GG: LHRH peptide was further modified by the addition of the lipid moiety Pam.sub.3 Cys. The lipid residue was covalently linked to the amino-terminus of peptide 18 prior to its cleavage from the resin used for synthesis of the peptide. Therefore, this modified peptide is organized in four linear domains, from the amino- to the carboxyl-terminus, as follows: tripalmitoyl-S-glycerol cysteine (Pam.sub.3 Cys), the hepatitis B surface antigen promiscuous helper T cell epitope (HBsAg T.sub.h), the glycine spacer (GG), and LHRH. This peptide is represented as follows: Pam.sub.3 Cys: HBsAg T.sub. : GG: LHRH. The lipid-modified peptide was formulated in the stable lipid emulsion, Liposyn (a mixture of emulsified soy bean and safflower oils) and administered subcutaneously to Sprague-Dawley rats. The dose used was the molar equivalent of 100 Mg of peptide 18 given at 0, 3 and 6 weeks. A second group of animals received unmodified peptide 18 in 100 Mg doses at 0, 3 and 6 weeks. 10 weeks following the initiation of the experiment, an ELISA assay was performed on sera from the immunized animals. 5 of 5 animals immunized with Pam.sub.3 Cys: HBsAg: GG: LHRH expressed significant anti-peptide 18 antibodies (OD>0.5 at a 1: 100 dilution). In contrast, none of the animals immunized with unmodified peptide 18 expressed antibodies to this level. Therefore, covalent lipid addition provides an effective means of potentiating immune responses.

Detailed Description Text - DETX (278):
The effects of mixing peptide A loaded microparticles in various adjuvant/emulsion formulations was examined. As can be seen in Table 7, certain formulations including Liposyn+Saponin and Squalene+L121 (4 of 6 animals in each group had atrophied testes) appear to improve the immune responses elicited by microparticulate peptide A. Liposyn is a soy bean oil and safflower oil emulsion prepared for intravenous feeding of humans, saponin

L15 ANSWER 1 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN

ACCESSION NUMBER: 2003197841 EMBASE

TITLE: Recombinant hepatitis B **vaccine** (**Engerix** -B.RTM.): A review of its immunogenicity and protective efficacy against hepatitis B.

AUTHOR: Keating G.M.; Noble S.; Averhoff F.M.; Belloni C.; Duval B.; Goldwater P.N.; Hall A.J.; Honorati M.C.; Kallinowski B.; Leroux-Roels G.; Poovorawan Y.

CORPORATE SOURCE: G.M. Keating, Adis International Limited, 41 Centorian Drive, Mairangi Bay, Auckland 10, New Zealand. demail@adis.co.nz

SOURCE: Drugs, (2003) 63/10 (1021-1051).
Refs: 250
ISSN: 0012-6667 CODEN: DRUGAY

COUNTRY: New Zealand

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 017 Public Health, Social Medicine and Epidemiology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB **Engerix**-B.RTM. (Hep-B[Eng]) is a noninfectious recombinant DNA **vaccine** containing hepatitis B surface antigen (HBsAg). It is produced from genetically engineered yeast (Saccharomyces cerevisiae). Intramuscular Hep-B(Eng) [0-, 1-, 6-month schedule] has excellent immunogenicity in healthy neonates and infants, children, adolescents and adults, with **seroprotection** rates of 85-100% seen .apprxeq.1 month after the final dose of **vaccine**; **seroprotection** was defined as an antibody against HBsAg (anti-HBs) titre of .gtoreq.10 IU/L. The use of alternative Hep-B(Eng) immunisation schedules (e.g. a 0-, 1-, 2-, 12-month schedule in neonates and infants, 0-, 12-, 24-month or two-dose schedules in children and adolescents, and accelerated schedules in adults) have also been associated with high rates of **seroprotection**. **Seroprotection** rates were generally similar with Hep-B(Eng) and the recombinant **vaccine** Recombivax HB.RTM. (Hep-B[Rax]) or plasma-derived **vaccines** (PDVs) .apprxeq.1 month after the final dose (although anti-HBs geometric mean titres were significantly higher with Hep-B[Eng] than with Hep-B[Rax]). One month after the final dose, adults had significantly higher **seroprotection** rates with the recombinant triple-antigen **vaccine** Bio-Hep-B.RTM. (Hep-B[Bio]) than with Hep-B(Eng), although **seroprotection** rates in healthy infants were similar with Hep-B(Eng) and Hep-B(Bio). Hep-B(Eng) had excellent immunogenicity in several groups considered at high risk of acquiring hepatitis B (e.g. neonates born to hepatitis B carrier mothers and healthcare workers). The immunogenicity of Hep-B(Eng) was reduced in patients with conditions associated with impaired immune function (e.g. patients undergoing haemodialysis or being treated for malignancy), although it had good immunogenicity in patients with diabetes mellitus. Hep-B(Eng) had excellent protective efficacy against HBsAg carriage in healthy infants and children, and in neonates born to hepatitis B carrier mothers (protective efficacy of 95-99%). Hep-B(Eng) also demonstrated good protective efficacy in a number of other high-risk groups. Hep-B(Eng) is generally well tolerated with a tolerability profile similar to that of Hep-B(Rax), Hep-B(Bio) and PDVs. In conclusion, Hep-B(Eng) is a well established, highly immunogenic hepatitis B **vaccine** with good tolerability and excellent protective efficacy; it offers flexibility through a variety of immunisation schedules. In addition, it appears that Hep-B(Eng) confers immunity for at least 10 years. Hep-B(Eng) has an important role in mass **vaccination** campaigns against hepatitis B, as well as in groups considered at high risk of acquiring hepatitis B.

My vaccine is a subunit mixture

L8 ANSWER 27 OF 44 MEDLINE on STN
ACCESSION NUMBER: 97451528 MEDLINE
DOCUMENT NUMBER: 97451528 PubMed ID: 9306481
TITLE: **Vaccine** antigen interactions after a **combination** diphtheria-tetanus toxoid-acellular pertussis/purified capsular polysaccharide of Haemophilus influenzae type b-tetanus toxoid **vaccine** in two-, four- and six-month-old infants.
AUTHOR: Pichichero M E; Latiolais T; Bernstein D I; Hosbach P; Christian E; Vidor E; Meschievitz C; Daum R S
CORPORATE SOURCE: University of Rochester, Elmwood Pediatrics, NY, USA.. mepo@uhura.cc.rochester.edu
SOURCE: PEDIATRIC INFECTIOUS DISEASE JOURNAL, (1997 Sep) 16 (9) 863-70.
Journal code: 8701858. ISSN: 0891-3668.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971103

AB OBJECTIVE: The safety and immunogenicity of a diphtheria-tetanus toxoid-acellular pertussis **vaccine** (DTaP; Trepedia)/Haemophilus influenzae b polysaccharide (PRP-T; ActHib) combined **vaccine** (TriHibir; Pasteur Merieux Connaught) was compared with DTaP and PRP-T given at the same visit but at separate sites in a prospective multicenter, open label trial. METHODS: Infants were randomized to four groups (three consistency lots of DTaP/PRP-T vs. one of the consistency lots given as separate **vaccines**); injections were administered at 2, 4 and 6 months of age. Pre-Dose 1 and post-Dose 3 sera were assayed for antibody titers against all antigens. Reactions to the **vaccinations** were assessed by parent questionnaire for 30 days after each injection visit. RESULTS: Four hundred eighty-five infants were enrolled; 296 evaluable infants were included in the DTaP/PRP-T group compared with 70 infants in the DTaP and PRP-T **vaccine** group. Infants who received the combined **vaccine** had higher post-Dose 3 geometric mean antibody titers to diphtheria antitoxin ($P < 0.01$) and pertussis filamentous hemagglutinin ($P < 0.05$) and lower geometric mean antibody titers to tetanus antitoxin ($P < 0.05$) and Haemophilus influenzae b (Hib) polysaccharide (PRP) ($P < 0.05$). The geometric mean anti-PRP antibody titer in the DTaP/PRP-T group was 4.3 micrograms/ml compared with 7.0 micrograms/ml in the separate **vaccine** group ($P < 0.05$), and the percentage of infants with antibody titers > or = 0.15 and 1 microgram/ml were, respectively, 95 and 86%, whereas they were 100% for both titers in the separate **vaccines** group. DTaP/ PRP-T **vaccine** given concomitantly or 1 month apart from **hepatitis** B **vaccine** and **oral** poliomyelitis **vaccine** caused no significant differences in immunogenicity or safety. The safety assessments for the DTaP/PRP-T **vaccine** showed no consistent differences in systemic or local injection site reactions compared with DTaP and PRP-T administered separately. CONCLUSION: Although the antibody responses to tetanus and Hib polysaccharide in the evaluated DTaP/PRP-T combined **vaccine** were significantly lower than those seen after separate DTaP and PRP-T administration, the combined **vaccine** elicited an immune response against diphtheria, tetanus, pertussis and Haemophilus influenzae b likely to confer protection.

L8 ANSWER 42 OF 44 MEDLINE on STN
ACCESSION NUMBER: 90030365 MEDLINE
DOCUMENT NUMBER: 90030365 PubMed ID: 2805046
TITLE: Immune response and reactions to simultaneous administration of **hepatitis** B **vaccine** with routine **vaccine** in children. I. Immune response and reactions to simultaneous administration of DPT, TOPV and **hepatitis** B **vaccine**.
AUTHOR: Yuan C D
SOURCE: CHUNG-HUA LIU HSING PING HSUEH TSA CHIH CHINESE JOURNAL OF EPIDEMIOLOGY, (1989 Aug) 10 (4) 206-9.
Journal code: 8208604. ISSN: 0254-6450.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198912
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19970203
Entered Medline: 19891218

AB This paper reports the result of the immune response and reactions to simultaneous administration of DPT, TOPV and **hepatitis** B **vaccine**. 180 children (0-5 months of age) were divided into three groups. Group one was **vaccinated** with **hepatitis** B **vaccine** alone, group two was **vaccinated** with DPT, TOPV **vaccine**, and group three was **vaccinated** with **hepatitis** B **vaccine**, DPT and TOPV **vaccine** simultaneously. The result of the immune response to the **combination** of **hepatitis** B with DPT, TOPV **vaccines** were similar to that observed after immunization with each **vaccine** alone. The general reactions of all **vaccines** were mild, no significant difference between each group was noted. The study demonstrated that children can be immunized with **hepatitis** B **vaccine** and DPT, TOPV **vaccines** simultaneously.

8 ANSWER 28 OF 44 MEDLINE on STN

ACCESSION NUMBER: 97383803 MEDLINE
DOCUMENT NUMBER: 97383803 PubMed ID: 9239772
TITLE: Inactivated poliovirus **vaccine** alone or sequential inactivated and **oral** poliovirus **vaccine** in two-, four- and six-month-old infants with **combination** Haemophilus influenzae type b/ **hepatitis** B **vaccine**.
AUTHOR: Halsey N A; Blatter M; Bader G; Thoms M L; Willingham F F; O'Donovan J C; Pakula L; Berut F; Reisinger K S; Meschievitz C
CORPORATE SOURCE: Department of International Health, Johns Hopkins University School of Public Health, Baltimore, MD 21205, USA.. nhalsey@phnet.sph.jhu.edu
SOURCE: PEDIATRIC INFECTIOUS DISEASE JOURNAL, (1997 Jul) 16 (7) 675-9.
Journal code: 8701858. ISSN: 0891-3668.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970916
Last Updated on STN: 19970916
Entered Medline: 19970904

AB BACKGROUND: Advisory committees have recommended the increased use of inactivated poliovirus **vaccine** (IPV) for children. OBJECTIVES: The purpose of this study was to assess the safety and immunogenicity of three schedules using IPV administered with diphtheria and tetanus toxoids and whole cell pertussis **vaccines** in a dual-chambered syringe. Children also received a **combination** of Haemophilus influenzae type b (Hib) and **hepatitis** B **vaccines** (COMVAX). METHODS: All infants ($n_{,}$ = 295) received IPV and COMVAX at 2 and 4 months of age and IPV, **oral** poliovirus **vaccine** (OPV) or both **vaccines** at 6 months and OPV at 15 months of age. RESULTS: After two doses of IPV 96 to 100% of infants had antibodies to poliomyelitis viruses types 1, 2 and 3, and after a third dose of **vaccine** (IPV or OPV) all but one child had antibodies to all three poliovirus types. After two doses of COMVAX 89 and 96% of children had protective levels of antibody to Hib and **hepatitis** B, respectively. CONCLUSIONS: IPV is highly immunogenic in a two-dose schedule. Administration of a third dose of IPV or a dose of OPV at 6 months of age is highly effective. Simultaneous administration of a **combination** H. influenzae type b/**hepatitis** B **vaccine** did not interfere with the response to IPV.

Foley, Shanon

To: Mosher, Mary
Subject: suggested claims for hepatitis case

Hi Mary. Yesterday, it looked like you couldn't administer an alum adjuvant mucosally, but today I found a post-filing date paper that does just that with HBsAg. I have noticed that all of the HBV vaccines I have come across use some form of adjuvant, such as alum, CpG, microparticles or acemannan. Also, alot of the vaccines are injected, which, like you said, can be squirted up the nose. Do you think they would buy:

42. An immunogenic formulation suitable for mucosal administration, **consisting of or consisting essentially of** a mixture of
(a) Hepatitis B virus surface antigen (HbsAG), and
(b) a second viral antigen which is a nucleocapsid protein ,
wherein the HbSag has an adjuvant effect upon the second antigen, and wherein said antigens are each present from 0.001mg to 1 mg.

to get rid of the adjuvant formulations?

or

42. An immunogenic formulation suitable for mucosal administration, comprising a mixture of
(a) Hepatitis B virus surface antigen (HbsAG), and
(b) a second viral antigen which is a nucleocapsid protein ,
wherein the HbSag has an adjuvant effect upon the second antigen, and wherein said antigens are each present from 0.001mg to 1 mg
and
(c) wherein the formulation does not comprise alum, CpG, microparticles or acemannan adjuvants.

OCUMENT NUMBER: 99012145 PubMed ID: 9796053
TITLE: Assessment of the immunogenicity and reactogenicity of a quadrivalent diphtheria, tetanus, acellular pertussis and **hepatitis** B (DTPa-HBV) **vaccine** administered in a single injection with Haemophilus influenzae type b conjugate **vaccine**, to infants at 2, 4 and 6 months of age.
AUTHOR: Aristegui J; Dal-Re R; Garrote E; Gonzalez A; Arrate J P; Perez A
CORPORATE SOURCE: Department of Pediatrics, Basurto Hospital, Bilbao, Spain.
SOURCE: VACCINE, (1998 Dec) 16 (20) 1976-81.
Journal code: 8406899. ISSN: 0264-410X.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981231

AB This double-blind, randomised study was performed to assess the immunogenicity and reactogenicity of three lots of a quadrivalent diphtheria-tetanus-acellular pertussis-**hepatitis** B **vaccine** (DTPa-HBV) co-administered with three lots of Haemophilus influenzae type b conjugate (Hib) **vaccine** in one injection, as a primary **vaccination** course in healthy infants at 2, 4 and 6 months of age. 269 infants (8-11 weeks of age) were randomly allocated to three groups to receive DTPa-HBV/Hib **vaccines**, concomitantly with **oral** polio **vaccine**. Blood samples for antibody determinations were taken before **vaccination** and 1 month after the third dose in 262 subjects. Local and general symptoms were recorded by parents on diary cards. All **vaccinees** had post-**vaccination** protective anti-D and anti-T (> or = 0.1 IU ml-1) antibodies, and 98% had protective anti-HBs antibody titres (> or = 10 mIU ml-1). There were no statistically significant differences between groups in post-**vaccination** anti-D, anti-T, anti-HBs antibody geometric mean titres (GMT), these being 3.49 IU ml-1, 5.92 IU ml-1 and 1109 mIU ml-1, respectively. All subjects responded to three pertussis components, i.e. pertussis toxin (PT), filamentous haemagglutinin (FHA) and pertactin (PRN). Although statistically significant differences in GMTs of anti-PT, anti-FHA and anti-PRN were found between groups, these were not believed to be of any clinical relevance as the minimum GMTs were 60, 193 and 230 EL.U ml-1 for anti-PT, anti-FHA and anti-PRN, respectively. There were no statistically significant differences in anti-PRP antibody GMT (4.05 micrograms ml-1) between groups, 100% and 85% of subjects having titres > or = 0.15 and 1.0 microgram ml-1, respectively. No symptoms were reported for one third of the subjects. Fever (> 38 degrees C) was reported after 16% of doses, with < 1% having > 39.5 degrees C. Almost all local and general symptoms were mild or moderate, and lasted less than 48 h. No subject dropped out due to a severe adverse reaction. The administration of an experimental **mix** of DTPa-HBV and Hib **vaccines** in a single injection is safe, well-tolerated and immunogenic for all **vaccine** components.

ACCESSION NUMBER: 1999012160 MEDLINE
DOCUMENT NUMBER: 99012160 PubMed ID: 9796068
TITLE: A combined liquid Hib (PRP-OMP), **hepatitis** B, diphtheria, tetanus and whole-cell pertussis **vaccine**: uncontrolled preliminary clinical trial of immunogenicity and reactogenicity.
AUTHOR: Nolan T; Hogg G; Darcy M A; Skeljo M; Carlin J
CORPORATE SOURCE: Melbourne University Department of Paediatrics, Royal Children's Hospital, Australia..
nolan@cryptic.rch.unimelb.edu.au
SOURCE: VACCINE, (1998 Dec) 16 (20) 2085-9.
Journal code: 8406899. ISSN: 0264-410X.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981231
AB We have conducted a preliminary uncontrolled clinical trial of the immunogenicity and reactogenicity of a new fully liquid pentavalent **combination vaccination** which incorporates a diphtheria, tetanus and whole-cell pertussis **vaccine** with Hib (PRP-OMP) and **hepatitis** B **vaccines**. Forty-five infants received three doses of the pentavalent **vaccination** at 2, 4, and 6 months of age, and then a fourth dose at 18 months of age. Subjects were bled prior to each **vaccination**, and a month after the third and fourth **vaccinations**. A 7-day diary card was used to record subject temperatures and other systemic and local clinical signs after each **vaccination**. After the third dose, 98% of subjects had anti-PRP titres above 1 microgram ml-1 (95%ci 88%, 100%). Following boosting, the geometric mean titre (GMT) rose a mean 27-fold (95%ci 19-fold, 38-fold) to 33 micrograms ml-1, and all subjects' titres (lower bound of 95%ci 92%) exceeded 1 microgram ml-1. For **hepatitis** B antibody, there was a GMT of 100 mIU ml-1 after the third dose, and 86% of infants (95%ci 73%, 95%) had antibody levels > or = 10 mIU ml-1. After the fourth dose, there was a mean 77-fold boost (95%ci 48-fold, 130-fold) to a GMT of 860 mIU ml-1 and 95% (95%ci 84%, 99%) of subjects had titres > or = 10 mIU ml-1. Diphtheria, tetanus, and pertussis antibody levels were all at acceptable levels after the first three doses and again after the fourth **vaccination**. The pentavalent **vaccine** was well tolerated at all administration times, and had a minor reactogenicity profile similar to DTPw alone as reported in previous studies. This study has provided preliminary evidence for both the safety and immunogenicity of the pentavalent **vaccine** given as a course at 2, 4, 6 and 18 months.

L8 ANSWER 11 OF 44 MEDLINE on STN
ACCESSION NUMBER: 2001243278 MEDLINE
DOCUMENT NUMBER: 21108996 PubMed ID: 11163669
TITLE: **Mucosal** immunization against **hepatitis** B virus by **intranasal** co-**administration** of recombinant **hepatitis** B surface antigen and recombinant cholera toxin B subunit as an adjuvant.
AUTHOR: Isaka M; Yasuda Y; Mizokami M; Kozuka S; Taniguchi T; Matano K; Maeyama J; Mizuno K; Morokuma K; Ohkuma K; Goto N; Tochikubo K
CORPORATE SOURCE: Department of Microbiology, Nagoya City University Medical School, Mizuho-ku, 467-8601, Nagoya, Japan.
SOURCE: VACCINE, (2001 Jan 8) 19 (11-12) 1460-6.
Journal code: 8406899. ISSN: 0264-410X.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010510

AB Recombinant cholera toxin B subunit (rCTB) produced by Bacillus brevis carrying pNU212-CTB has been previously found to be a potent **mucosal** adjuvant to aluminium-non-adsorbed tetanus toxoid (nTT) and diphtheria toxoid (nDT) co-administered intranasally, and the possibility of needle-free inoculation of these **vaccines** with rCTB has been suggested. In this paper we examined the potentiality of rCTB as a **mucosal** adjuvant to aluminium-non-adsorbed yeast-derived recombinant **hepatitis** B surface antigen (rHBs) being a particulate antigen when administered intranasally with rCTB. In-house ELISA showed that a **mixture** of rHBs (1 or 5 microg) and rCTB (10 microg) elevated not only systemic responses but also **mucosal** immune responses at the **nasal** cavity, the lung, the saliva, the small intestine and the vagina against rHBs, and these could be further increased with higher doses of antigen. With antibody isotypes of IgG, there were equally high levels of serum HBs-specific IgG1, IgG2a and IgG2b antibodies and induction of **mixed** Th1- and Th2-type responses was considered to occur in **combination** of rHBs and rCTB. Serum anti-HBs titres in almost all mice obtained from sandwich EIA using a commercial kit were higher than 1000 milli-international units ml(-1) (mIU ml(-1)). These results show that rCTB is also very effective as a **mucosal** adjuvant for a particulate antigen like rHBs, as well as soluble antigens like nTT and nDT reported previously, suggesting the possibility of **intranasal** immunization with rHBs plus rCTB in humans.

L8 ANSWER 9 OF 44 MEDLINE on STN
ACCESSION NUMBER: 2002201989 MEDLINE
DOCUMENT NUMBER: 21932489 PubMed ID: 11934561
TITLE: Parenteral and **mucosal** prime-boost immunization strategies in mice with **hepatitis** B surface antigen and CpG DNA.
AUTHOR: McCluskie Michael J; Weeratna Risini D; Payette Paul J; Davis Heather L
CORPORATE SOURCE: Coley Pharmaceutical Group, 725 Parkdale Avenue, K1Y 4E9, Ottawa, ON, Canada.. mmccluskie@coleypharma.com
SOURCE: FEMS IMMUNOLOGY AND MEDICAL MICROBIOLOGY, (2002 Feb 18) 32 (3) 179-85.
Journal code: 9315554. ISSN: 0928-8244.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020406
Last Updated on STN: 20020702
Entered Medline: 20020701

AB Synthetic oligodeoxynucleotides (ODN) containing immunostimulatory CpG motifs (CpG ODN) are potent adjuvants to protein antigens administered by parenteral or **mucosal** routes to BALB/c mice. To date, there have been no studies using combined parenteral/**mucosal** approaches with CpG DNA as adjuvant. In this study we evaluated different parenteral prime-**mucosal** boost and **mucosal** prime-parenteral boost strategies using **hepatitis** B surface antigen (HBsAg) alone or with different adjuvants: aluminum hydroxide (alum), cholera toxin (CT), CpG ODN. In addition, since CpG ODN has previously been shown to act synergistically with other adjuvants after parenteral or **mucosal** delivery, we also evaluated adjuvant **combinations**: alum+CpG ODN and CT+CpG ODN. The effects of adjuvant and **administration** strategy on systemic and **mucosal** humoral responses were measured, as well as cell-mediated immune responses (cytotoxic T lymphocyte activity). These results were compared to parenteral only or **mucosal** only strategies. Our findings demonstrate that parenteral immunization can prime for **mucosal** responses even when different lymph nodes were being targeted. HBsAg-specific immune responses (IgG in plasma, cytotoxic T lymphocytes) induced by parenteral prime could all be significantly enhanced by **mucosal** boosting and despite the fact that intramuscular immunization alone could not induce **mucosal** IgA, it could prime for a subsequent **mucosal** boost. In addition, the presence of adjuvant at time of boosting could influence the nature of subsequent immune responses (Th1 vs. Th2). Mice primed intranasally could have their systemic immune responses boosted with a parenteral **administration** and it was also possible to enhance **mucosal** responses induced by **intranasal** prime with an intramuscular boost.

QR 180.T52

6/7/52
DIALOG(R)File 155:MEDLINE(R)

06166142 89181627 PMID: 2467197
Hepatitis B virus surface antigen (HBsAg) as carrier for synthetic peptides having an attached hydrophobic tail.
Neurath A R; Strick N; Girard M
Lindsley F. Kimball Research Institute, New York Blood Center, NY 10021.
Molecular immunology (ENGLAND) Jan 1989, 26 (1) p53-62, ISSN 0161-5890 Journal Code: 7905289
Contract/Grant No.: CA43315; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
B- and T-cell epitopes from three distinct regions of the hepatitis B virus (HBV) envelope (env) protein (preS1, preS2 and S) are involved in eliciting protective immunity. Since preS1 sequences inhibit the secretion of HBV env proteins from eukaryotic cells, it is difficult to prepare immunogens rich in preS1 sequences. This problem can be overcome by linking synthetic peptides from the preS1 region to particles containing both S and preS2 sequences. We describe here a novel approach for binding of synthetic peptides to exposed hydrophobic domains on HBV env proteins. Long chain fatty acids or mercaptans are covalently linked to synthetic peptides. Peptides with the attached hydrophobic tails interact strongly with HBV env proteins (S + preS2), whereby hybrid immunogens are generated. Such immunogens can be used in combination with alum, the only adjuvant approved for human use. The combination of the preS1 peptide [preS(12-47)] with particles containing the S and preS2 regions resulted in an immunogen which: (1) elicits a broad spectrum of protective antibodies; (2) circumvents the nonresponsiveness to: (a) preS1 epitopes in preS1-nonresponder strains of mice; and (b) S-protein in S-protein-nonresponder strains of mice; and (3) augments the immune response to S-protein. The combination of HBV env proteins with a synthetic peptide from the envelope of the human immunodeficiency virus (HIV-1) resulted in an immunogen eliciting anti-HIV-1. Hybrid immunogens consisting of viral proteins and of synthetic peptides represent a feasible approach for the design of future vaccines.
Record Date Created: 19890425
Record Date Completed: 19890425
?

ACCESSION NUMBER: 97092930 EMBASE
DOCUMENT NUMBER: 1997092930
TITLE: Enhanced lymph node delivery and immunogenicity of hepatitis B surface antigen entrapped in galactosylated liposomes.
AUTHOR: Kim C.-K.; Jeong E.J.
CORPORATE SOURCE: C.-K. Kim, College of Pharmacy, Seoul National University, San 56-1, Shinlin-Dong, Kwanak-Ku, Seoul 151-742, Korea, Republic of
SOURCE: International Journal of Pharmaceutics, (1997) 147/2 (143-151).
Refs: 19
ISSN: 0378-5173 CODEN: IJPHDE
PUBLISHER IDENT.: S 0378-5173(96)04798-9
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The purpose of this work is to increase the lymph node delivery and the immunogenicity of hepatitis B surface antigen (HBsAg) in vivo. HBsAg was entrapped in the dried liposomes with their surfaces modified with galactose. Pharmacokinetics and organ distribution of free HBsAg alone, HBsAg mixed with **aluminum phosphate, HBsAg** entrapped in ungalactosylated liposomes and galactosylated liposomes (GalL) were studied. For each sample, the anti-HBsAg titres were measured by RIA. Most HBsAg in GalL, existed in an antibody-available form. In rats, HBsAg in GalL administered to right thigh muscles, resided in the injection sites longer than did free HBsAg alone or HBsAg mixed with aluminum phosphate. Also, GalL delivered higher amounts of HBsAg to the regional lymph nodes than did other formulations: the area under the concentration-time curve of HBsAg in the regional lymph nodes given in GalL was 16, 2.4, and 2.2-fold higher than that in free form, aluminum phosphate mixture and ungalactosylated liposomes, respectively. The immunogenicity of HBsAg given in GalL showed a good correlation to its enhanced delivery to the lymph nodes. HBsAg in GalL boosted the formation of antibodies 40-fold higher than did free HBsAg, whereas HBsAg mixed with aluminum phosphate and HBsAg in ungalactosylated liposomes increased the titre by 21- and 13-fold, respectively. Taken together, it is concluded that the galactosylated liposomes can target HBsAg to the regional lymph nodes, rich in the antigen-presenting cells and enhance the immunogenicity of HBsAg more efficiently than do the conventional aluminum phosphate or the ungalactosylated liposome formulations.

6/7/15
DIALOG(R)File 155:MEDLINE(R)

09968980 21893407 PMID: 11895556

Therapeutic vaccination in chronic hepatitis B.

Senturk Hakan; Tabak Fehmi; Akdogan Meral; Erdem Levent; Mert Ali; Ozaras Resat; Sander Ersan; Ozbay Gulsen; Badur Selim

Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Turkey. haksen@escortnet.com

Journal of gastroenterology and hepatology (Australia) Jan 2002, 17 (1) p72-6, ISSN 0815-9319 Journal Code: 8607909

Document type: Clinical Trial; Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

AIMS: The aim was to test the efficacy of a pre-S2-containing vaccine (Genhevac-B) in chronic hepatitis B (CHB). Twenty-five naive patients (22 male, three female; median age 35; range: 6-69 years) with CHB were recruited. The inclusion criteria were: hepatitis B e antigen (HBeAg) positive or HBV-DNA detectable with liquid hybridization; alanine aminotransferase (ALT) is at least 1.5-fold the upper normal limit and histological evidence of chronic hepatitis. METHODS: In the first period, all patients received monthly injections of 20, 40 and 60 microg of the vaccine. One month after the last injection, patients who still had HBV-DNA were divided into two randomly assigned groups. While the patients in the first group and the patients who lost HBV-DNA in the first period continued to receive monthly injections of 20 microg vaccine for a further 6 months, the patients in the second group received 9 MU interferon alpha-2b (Roferon-A), three times per week using the same method as for the first group. Patients were followed up after 12 months without treatment. Response was defined as the loss of HBV-DNA and normalization of ALT. RESULTS: Six of the 25 patients lost HBV-DNA after 3 months. Nine of the remainder were randomly placed in the first group (vaccine-only) and 10 were placed in the second group (vaccine + interferon). End-of-treatment response was achieved, overall, 8/15 from the vaccine group and 6/10 from the combination. One patient from each group relapsed during the follow up. Overall, the sustained response (SR) rate was 46% (7/15) in the vaccine group, and 50% (5/10) in the combination group. Histological improvement was achieved in 6/7 SR with vaccine-only and all five with combination treatment, while 1/8 of failures of vaccine and 2/5 of failures of combination improved. CONCLUSIONS: It was concluded that Genhevac-B decreases serum HBV-DNA levels in the majority of patients with CHB and sustained clearance was achieved in some patients. Combination of interferon-alpha with Genhevac-B is effective for the vaccine failures and may increase sustained response compared to interferon-alpha alone. However, the mechanism of action is yet to be explained.

Record Date Created: 20020315

Record Date Completed: 20020617